METHOD OF PREPARING (3R,3aS,6aR)-3-HYDROXYHEXAHYDROFURO[2,3-b]FURAN AND RELATED COMPOUNDS

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. provisional patent application Serial No. 60/417,379, filed October 9, 2002.

STATEMENT OF GOVERNMENTAL INTEREST

FIELD OF THE INVENTION

The present invention is directed to methods of preparing (3R,3aS,6aR)-3-hydroxyhexahydrofuro[2,3-b]furan, having a structural formula (I), stereoisomers of (I), and compounds structurally related to (I).

(I)
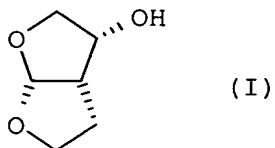
The present invention also is directed to a method of preparing (5S)-5-(benzyloxymethyl)-5H-furan-2-one having a structure
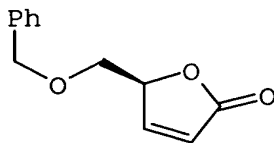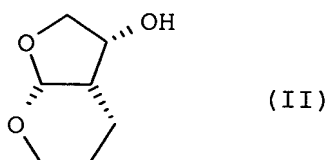
BACKGROUND OF THE INVENTION

Significant advances have been made in the design and synthesis of nonpeptidal ligands for the HIV protease substrate binding site. See, S. Thaisrivong, *Annual Reports on Med. Chem.*, *29,* p. 133 (1994). The structure-based design of bis-tetrahydrofuran ligands that can effectively replace two amide bonds and a 10π-aromatic system of an HIV protease inhibitor has been reported (A.K. Ghosh et al., *J. Med. Chem.*, *37,* p. 2506 (1994)).
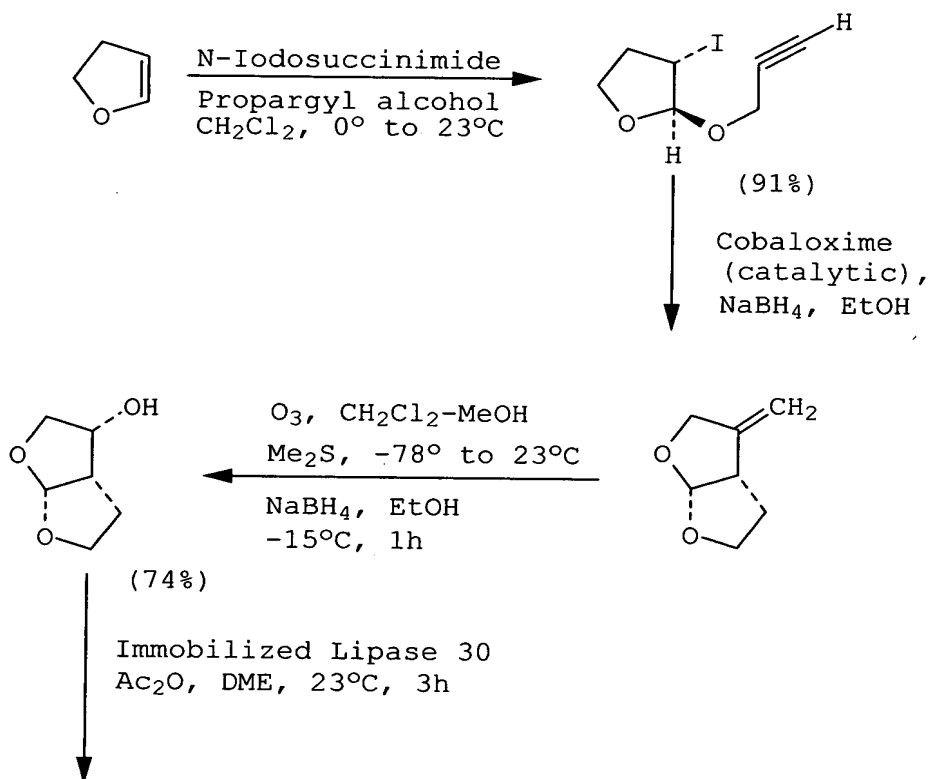
The present commercial method of synthesizing the compound of structural formula (I) provides a racemic mixture, which requires enzymatic resolution to provide optically active ligands with high enantiomeric excess. The preparation of a racemic mixture, and subsequent resolution to provide compound (I), significantly reduces the yield of the desired enantiomer because about one-half of the racemic mixture, i.e., the undesired enantiomer, is wasted. In addition, costs are increased because about one-half of the starting materials and reagents used in the synthesis are wasted.

In particular, the following synthetic scheme (1) illustrates the present commercial method of synthesizing compound (I). This synthesis is disclosed in detail in A.K. Ghosh et al., *Tetra-*

hedron Letters, 36(4), pp. 505-508 (1995), incor-
porated herein by reference. Also see, A.K. Ghosh
et al., *J. Med. Chem., 39*, pp. 3278-3290 (1996) for
the synthesis of compound (I) and a related compound
of structural formula (II) (i.e., (3S,3aR,7aS)-3-
hydroxyhexahydrofuro[2,3-b]pyran).

(II)

Scheme 1
(prior art)

(42%)   +   (45%)

(I)

Aq. LiOH   R=Ac
            R=H

Alternatively,

Immobilized
Lipase 30

pH 7 buffer
23°C, 24 h

(±)

(34%)   +   (40%)

MeLi, THF   R=Ac
             R=H   (Compound (I))
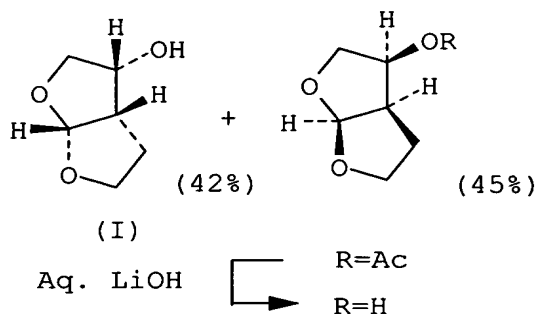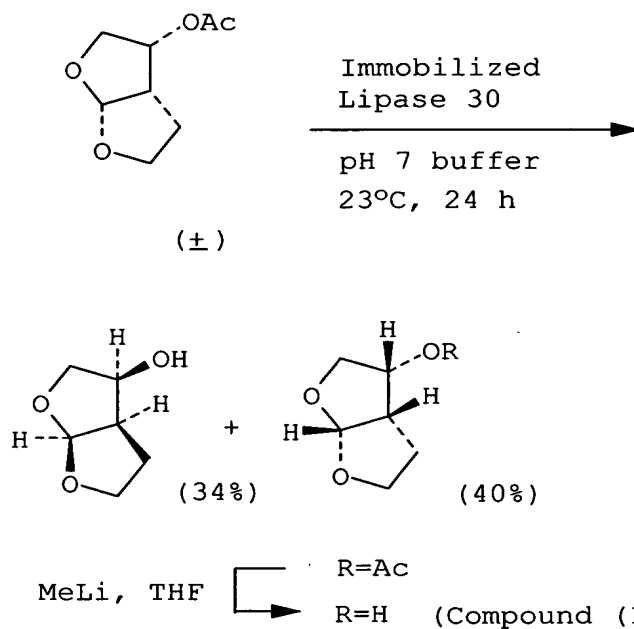
There is a need in the art to provide an improved method of synthesizing compound (I), stereoisomers of (I), and related compounds, like compound (II). In particular, a need exists for a short synthetic route that avoids generation of a racemic mixture, and, therefore, increases yield of the desired enantiomer and decreases costs.

There also is a need in the art for an improved synthesis of precursors to compound (I), for example (5S)-5-(benzyloxymethyl)-5H-furan-2-one.

SUMMARY OF THE INVENTION

The present invention relates to methods of preparing (3R,3aS,6aR)-3-hydroxyhexahydrofuro-[2,3-b]furan and related compounds, and to a method of preparing a precursor to compound (I). In particular, the present invention relates to a stereoselective method preparing a compound of structural formula (I), stereoisomers of (I), and related compounds, like the compound of structural formula (II). The present method overcomes disadvantages associated with the present-day commercial synthesis of compound (I), e.g., eliminates the enzymatic resolution of a racemic mixture and increases the yield of the desired enantiomer. The present invention also provides a method of preparing a precursor to compound (I) in high stereoselective yield.
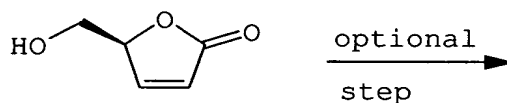
In particular, the present invention is directed to a new and convenient synthesis of (3R,3aS,6aR)-3-hydroxyhexahydrofuro[2,3-b]furan, also termed bis-THF and compound (I), which is an important ligand for several highly potent HIV protease inhibitors, including
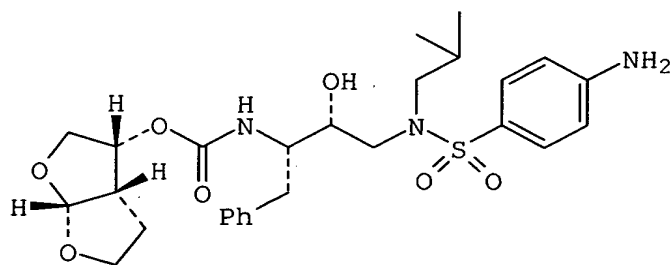
(III)

The method disclosed herein is a new and economical synthesis of an important P_2 ligand, i.e., bis-THF, and ligands related in structure to bis-THF. Incorporation of bis-THF in various dipeptide isosteres, including (R)-(hydroxyethyl)aminosulfonamide isosteres, resulted in enhanced potency against wild-type HIV protease, and also against numerous mutant proteases isolated from drug-resistant HIV. The present method also allows (a) synthesis of stereoisomers of bis-THF, (b) incorporation of substituents onto the bis-THF ring system, and (c) variation of ring sizes to optimize HIV protease inhibitor properties, including *in vitro* potency, *in vivo* potency, and oral bioavailability.

The present method of synthesizing bis-THF is summarized as follows:

(78-100%)

hv

PG—O

(70-90%)

LiAlH$_4$
Et$_2$O, 0°C
2-3 h

THF:H$_2$O (5:1)

pH 2-3
23°C, 12 h

(65-80%)

1. TPAP, MNO
   5-10 min

2. NaBH$_4$, EtOH
   -15°C, 1-3 h

(65-75%)
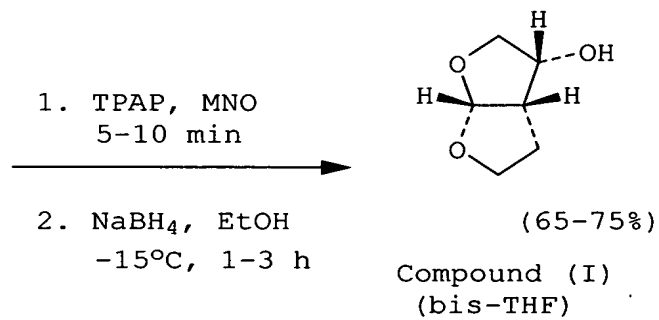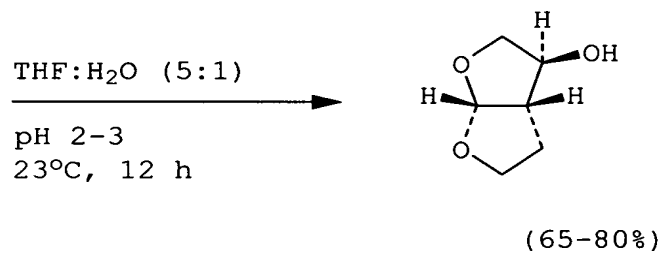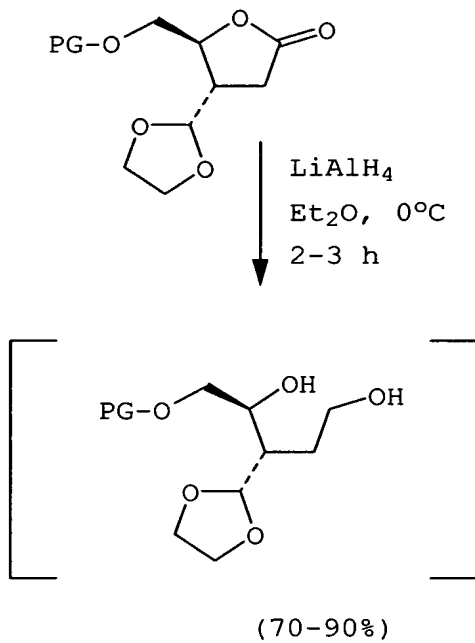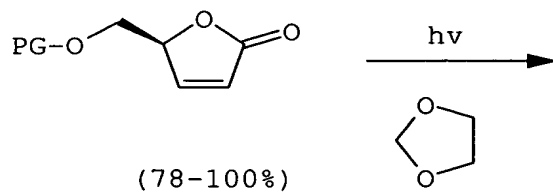
Compound (I)
(bis-THF)

Another aspect of the present invention is to provide a method of preparing a compound having a structure

$$C_6H_5CH_2-O \diagup \overset{O}{\diagdown} \diagup \diagup O$$

,
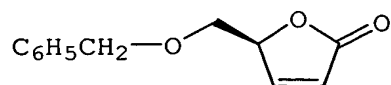
then utilizing the benzyl-protected 5-hydroxymethyl-5H-furan-2-one in the synthesis of compound (I).

Another aspect of the present invention is to provide a method of preparing compounds related to bis-THF by using a starting material having a following structure:
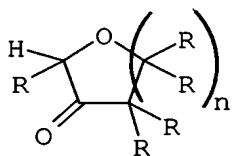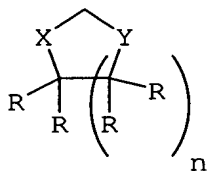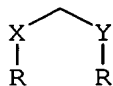
$$\left(\underset{R}{\overset{X}{\diagup}} \diagup \underset{R}{\overset{Y}{\diagdown}} R \right)_n$$

,

$$\left(\underset{O}{\overset{H}{\diagup}} R \diagup \underset{R}{\overset{O}{\diagdown}} \underset{R}{\overset{R}{\diagdown}} \right)_n$$

, or

$$\underset{R}{\overset{X}{|}} \diagup \underset{R}{\overset{Y}{|}}$$

,

wherein X and Y, independently, are selected from the group consisting of O, S, and NR; each R, independently, is selected from the group con-

sisting of hydro, C_{1-4}alkyl, aryl, C_{1-3}alkoxy, C_{1-2}-alkylenearyl; and n is 1, 2, or 3.

Another aspect of the present invention is to provide a method of synthesizing various stereo-isomers of bis-THF and compounds related to bis-THF in high stereospecific yield.

In addition, the present invention is directed to methods of preparing protected (5R)-hydroxymethyl-5H-furan-2-ones, such as (5S)-5-(benzyloxymethyl)-5H-furan-2-one.

These and other novel aspects and advan-tages of the present invention will become apparent from the following detailed description of the pre-ferred embodiments.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is directed to an efficient, enantioselective synthesis of (3R,3aS,6aR)-3-hydroxyhexahydrofuro[2,3-b]furan (i.e., compound (I) or bis-THF), which is a ligand used in the synthesis of several potent HIV protease inhibitors. For example, compound (III) is current-ly in clinical trials and contains bis-THF as the P_2 ligand. The bis-THF ligand also can be utilized as a component of other therapeutic compounds. The present invention further is directed to methods of synthesizing stereoisomers of bis-THF and synthesiz-ing bicyclic ligands related in structure to bis-THF in high stereospecific yield.

In addition, the present invention is directed to methods of preparing protected (5R)-

hydroxymethyl-5H-furan-2-ones, such as (5S)-5-(benzyloxymethyl)-5H-furan-2-one.

The present-day synthesis of bis-THF involves four steps, and yields bis-THF in racemic form. An enzymatic optical resolution of the racemic product provides the desired biologically more active ligand (i.e., bis-THF). The other, less biologically active enantiomer has little value. Thus, the overall synthesis of bis-THF is inefficient. The present synthetic route produces a single, optically pure enantiomer. The present synthetic route also utilizes readily available starting materials, as well as a very efficient, high yield photochemical step.

The present disclosure focuses on the synthetic route to provide bis-THF. However, as disclosed hereafter, substituting a different heterocyclic starting material for 1,3-dioxolane yields compounds related to bis-THF, stereoselectively and in good yield, using the identical synthetic route. The compounds related to bis-THF also can be used as ligands in pharmaceutical compounds, like HIV protease inhibitors. In addition, stereoisomers of bis-THF can be prepared by starting with a different enantiomer of hydroxymethyl-5H-furan-2-one.

The following abbreviations are used in this specification: CH_2Cl_2 (methylene chloride), $NaBH_4$ (sodium borohydride), EtOH (ethanol), MeOH (methanol), Me_2S (dimethyl sulfide), h (hour), Ac (acetyl), Ac_2O (acetic anhydride), DME (dimethoxyethane), LiOH (lithium hydroxide), Et_3N (trimethyl-

amine), MeLi (methyl lithium), THF (tetrahydro-
furan), PG (protecting group), hν (light), LiAlH$_4$
(lithium aluminum hydride), Et$_2$O (diethyl ether), H$_2$O
(water), TPAP (tetrapropylammonium perruthenate),
MNO (4-methylmorpholine-N-oxide), min (minute), RT
(room temperature), MS (molecular sieve), t-Bu
(tertiary butyl), Na$_2$SO$_4$ (sodium sulfate), CHCl$_3$
(chloroform), CDCl$_3$ (deuterated chloroform), NaHCO$_3$
(sodium bicarbonate), Ph (phenyl), g (gram), and
NH$_4$Cl (ammonium chloride).

The synthesis of bis-THF (compound (I)) is
summarized below:

$$\text{NaBH}_4 \quad \text{EtOH} \quad -15°C, \; 1-3 \; h$$

(I)
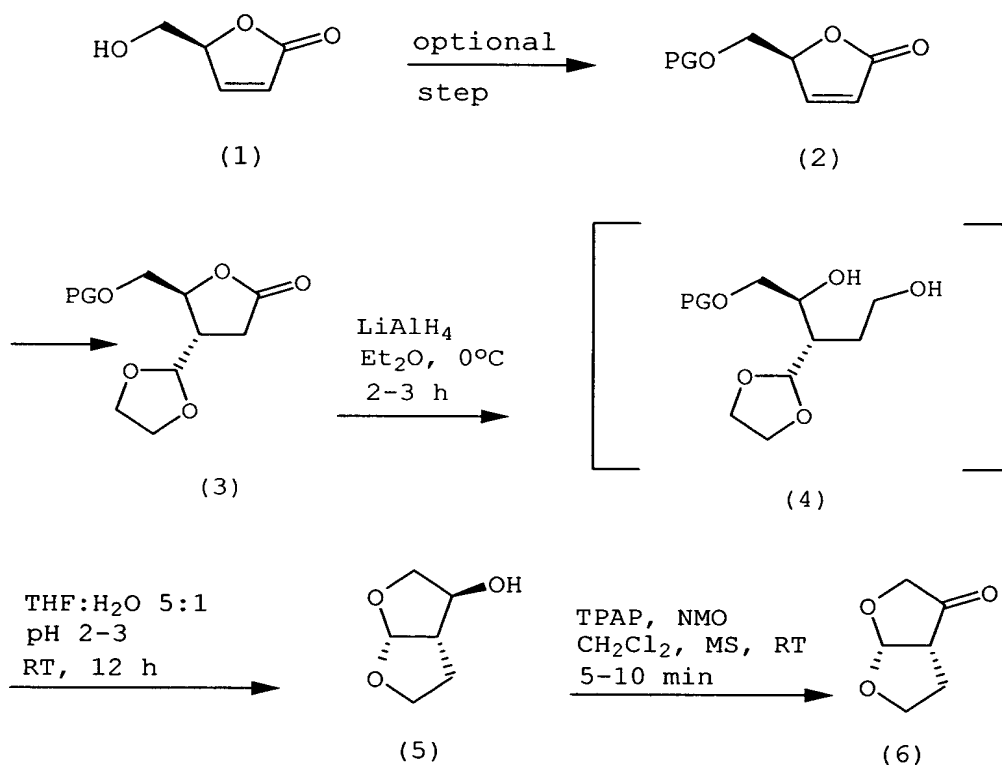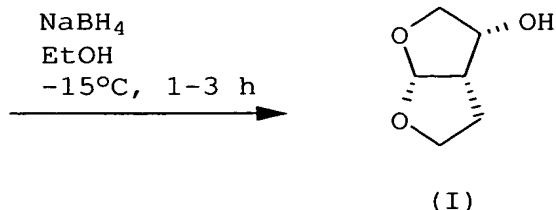
The starting material for the present synthetic route to compound (I) is (5S)-hydroxymethyl-5H-furan-2-one (1). In the first step of the synthesis, the hydroxy group of compound (1) optionally is protected by reacting compound (1) with compound capable of positioning a protecting group (PG) at the hydroxy position of compound (1). This step can be eliminated, and compound (1) can be converted directly to an unprotected compound (3), e.g., PG is H. In some embodiments, use of a PG compound is preferred because subsequent reaction products are easier to isolate.

Protecting group (PG) compounds are utilized in accordance with general principles of synthetic organic chemistry. The identity of the PG compound is not limited and can be any protecting group known to persons skilled in the art. Numerous PG compounds are disclosed in Greene et al., eds., "Protective Groups in Organic Synthesis," Third Edition, John Wiley and Sons, NY, NY (1999) incorporated herein by reference. The protecting groups are removed when necessary by appropriate basic, acidic, or hydrogenolytic conditions known to persons skilled in the art. Accordingly, a compound (2) not specifically exemplified herein can be pre-

pared by persons skilled in the art. A typical compound capable of positioning a PG at the hydroxy position of compound (1) is an acid chloride, a trialkylsilyl chloride, or dihydropyran.

The following examples illustrate the synthesis of optional protected compounds (2) using various PG compounds.

5-(tert-Butyldimethylsilanyloxymethyl)-5H-furan-2-one (2a)
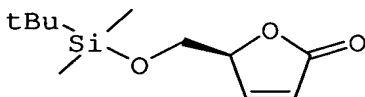
(5S)-5-(tert-Butyldimethylsilanyloxymethyl)-5H-furan-2-one (2a): To a solution containing 199 mg (1.74 mmol) (5S)-hydroxymethyl-5H-furan-2-one (1) and 178 mg (2.61 mmol) imidazole in 10 mL CH_2Cl_2, at 0°C, was added 342 mg (2.27 mmol) of tert-butyldimethylsilyl chloride (TBDMS) in one portion. The resulting mixture was stirred for 30 minutes at 0°C. After warming to room temperature, stirring was continued for another 30 minutes. Then 40 mL of water was added, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL), and the combined organic extracts were dried over Na_2SO_4. Evaporation of the solvent followed by column chromatography (silica gel 50 g, ethyl acetate in hexanes 20%) yielded compound (2a) (398 mg, 100%) as a colorless solid, R_f=0.24, $[\alpha]^{25}_D$-137°, c 0.9, $CHCl_3$, IR (neat) 2929, 1755, 1256, 837

cm^{-1}; ^{1}H-NMR (500 MHz, CDCl$_3$) δ: 0.06 (s, 6H), 0.87 (s, 9H), 3.79 (dd, 1H, J=5.5 Hz, J=10.8 Hz), 3.92 (dd, 1H, J=4.5 Hz, J=10.8 Hz), 5.05 (m$_c$, 1H), 6.16 (dd, 1H, J=1.2 Hz, J=4.5 Hz), 7.49 (dd, 1H, J=1.2 Hz, J=5.5 Hz). ^{13}C-NMR (125.8 MHz, CDCl$_3$, Dept) δ: -5.11 (+), 18.63 (quat), 26.13 (+), 63.33 (-), 83.75 (+), 122.94 (+), 154.75 (+), 173.39 (quat). C$_{11}$H$_{20}$O$_3$Si; Exact Mass: 228.12; Mol. Wt.: 228.36; C, 57.85; H, 8.83; O, 21.0; Si, 12.30.

Acetic acid 5-oxo-2,5-dihydro-furan-2-ylmethyl ester (2c)
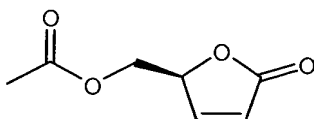
(5S)-5-(Acetyloxymethyl)-5H-furan-2-one (2c): To a solution containing 1.012 g (8.869 mmol) (5S)-hydroxymethyl-5H-furan-2-one (1) in 50 mL of dry pyridine, at 0°C, was added a solution containing 0.631 mL (8.87 mmol) acetyl chloride in 10 mL CH$_2$Cl$_2$. After stirring for 1 hour at 0°C, the solvent was removed. The residue was dissolved in the CH$_2$Cl$_2$ (50 mL) and was washed with saturated NaHCO$_3$ solution (50 mL). The organic layer was separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 50 mL), and the combined organic extracts were dried over Na$_2$SO$_4$. Evaporation of the solvent followed by column chromatography (silica gel 100 g, ethyl acetate in hexanes 50%) yielded compound (2c) (1.27 g, 92%) as a colorless solid, R$_f$=0.31, [α]$^{25}_D$ -134.5°, c 1.3, CHCl$_3$, IR (neat) 1746, 1367, 1218, 767 cm^{-1}; ^{1}H-

NMR (300 MHz, CDCl$_3$) δ: 2.05 (s, 3H), 4.32 (m, 2H), 5.23 (m, 1H), 6.20 (dd, 1H, J=2.2 Hz, J=5.8 Hz), 7.43 (dd, 1H, J=1.6 Hz, J=5.8 Hz). ^{13}C-NMR (75.4 MHz, CDCl$_3$, Dept) δ: 20.58 (+), 62.55 (-), 80.74 (+), 123.32 (+), 152.32 (+), 170.51 (quat), 172.22 (quat). C$_7$H$_8$O$_4$; Exact Mass: 156.04; Mol. Wt.: 156.14; C, 53.85; H, 5.16; O, 40.99.

(5S)-5-Pivaloyloxymethyl)-5H-furan-2-one (2d)
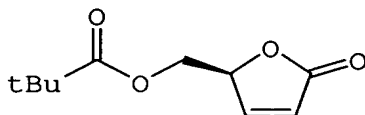
(5S)-5-(Pivaloyloxymethyl)-5H-furan-2-one (2d): To a solution containing 101 mg (0.885 mmol) (5S)-hydroxymethyl-5H-furan-2-one (1) in 10 mL of dry CH$_2$Cl$_2$ and 79 μL (0.97 mmol) pyridine, at 0°C, was added a solution containing 120 μL (0.973 mmol) pivaloyl chloride in 2 mL CH$_2$Cl$_2$. After stirring for 3 hours at 0°C, the solution was stirred at room temperature overnight. The solvent then was removed, and the residue was dissolved in CH$_2$Cl$_2$ (10 mL) and washed with saturated NaHCO$_3$ solution (5 mL). The organic layer was separated, the aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 10 mL), and the combined organic extracts dried over Na$_2$SO$_4$. Evaporation of the solvent followed by column chromatography (silica gel 30 g, ethyl acetate in hexanes 40%) yielded compound (2d) (143 mg, 81%) as a colorless solid, R$_f$=0.20, [α]$^{25}_D$ -138°, c 1.3, CHCl$_3$, IR

(neat) 3056, 1756, 1730, 1616, 1172 cm^{-1}; ^{1}H-NMR (300 MHz, CDCl$_3$) δ: 1.16 (s, 9H), 4.36 (d, 2H, J=4.2 Hz), 5.23 (dd, 1H, J=1.8 Hz, J=4.2 Hz), 6.18 (dd, 1H, J=1.8 Hz, J=5.4 Hz), 7.42 (dd, 1H, J=1.8 Hz, J=5.4 Hz). ^{13}C-NMR (75.4 MHz, CDCl$_3$, Dept) δ: 26.76 (+), 38.58 (quat), 61.68 (-), 80.78 (+), 122.98 (+), 152.21 (+), 172.03 (quat), 177.76 (quat). C$_{10}$H$_{14}$O$_4$; Exact Mass: 198.09; Mol. Wt.: 198.22; C, 60.59; H, 7.12; O, 32.29.

Benzoic acid 5-oxo-2,5-dihydro-furan-2-ylmethyl ester (2e)
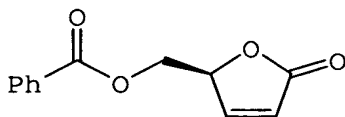
(5S)-5-(Benzoyloxymethyl)-5H-furan-2-one (2e): To a solution containing 94 mg (0.82 mmol) (5S)-hydroxymethyl-5H-furan-2-one (1) in 10 mL of dry pyridine, at 0°C, was added a solution containing 96 μL (0.82 mmol) benzoyl chloride in 1.5 mL CH$_2$Cl$_2$. After stirring for 1 hour at 0°C, the solvent was removed, and the residue was dissolved in CH$_2$Cl$_2$ (10 mL) and washed with saturated sodium NaHCO$_3$ (5 mL). The organic layer was separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 10 mL), and the combined organic extracts were dried over Na$_2$SO$_4$. Evaporation of the solvent followed by column chromatography (silica gel 35 g, ethyl acetate in hexanes 40%) yielded compound (2e) (154 mg, 86%) as a colorless solid, R$_f$=0.30, [α]$^{25}_D$ -119.1°, c

0.8, CHCl₃, IR (neat) 1787, 1762, 1772, 1271, 771 cm¹; ¹H-NMR (300 MHz, CDCl₃) δ: 4.57 (dd, 2H, J=4.2 Hz, J=9.0 Hz), 5.34 (m, 1H), 6.17 (dd, 1H, J=1.8 Hz, J=5.4 Hz), 7.41 (m, 2H), 7.51 (m, 2H), 7.93 (dd, J=5.1 Hz, J=6.9 Hz). ¹³C-NMR (75.4 MHz, CDCl₃, Dept) δ: 62.61 (+), 80.71 (-), 123.07 (+), 128.27 (+), 128.81 (quat), 129.37 (+), 133.25 (+), 152.46 (+), 165.69 (quat), 172.10 (quat). C₁₂H₁₀O₄; Exact Mass: 218.06; Mol. Wt.: 218.21; C, 66.05; H, 4.62; O, 29.33

5-(Tetrahydro-pyran-2-yloxymethyl)-5H-furan-2-one (2f)
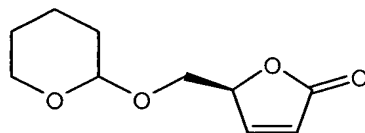
(5S)-5-(Tetrahydropyran-2-yloxymethyl)-5H-furan-2-one (2f): To a solution containing 100.1 mg (0.877 mmol) (5S)-hydroxymethyl-5H-furan-2-one (1) in 10 mL of CH₂Cl₂ was added, at room temperature, 88 μL (0.97 mmol) dihydropyran and 10 mg (0.053 mmol) p-toluenesulfonic acid. After 8 hours, a saturated NaHCO₃ solution (5 mL) was added. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic extracts were dried over Na₂SO₄. Evaporation of the solvent followed by column chromatography (silica gel 30 g, ethyl acetate in hexanes 60%) yielded compound (2f) (136 mg, 78%) as a colorless solid, Rf=0.23, [α]²⁵D -129°, c 0.8, CHCl₃; ¹H-NMR (300 MHz,

CDCl$_3$) δ: 1.20-1.80 (m, 6H), 3.41-3.51 (m, 1H),
3.58-3.62 (m, 1H), 3.67-3.81 (m, 1H), 3.82-3.95 (m,
1H), 4.56-4.58 (m, 0.5H), 4.60-4.63 (m, 0.5H), 5.15-
5.19 (m, 1H), 6.13-6.15 (m, 1H), 7.49-7.51 (m, 1H).
C$_{10}$H$_{14}$O$_4$; Exact Mass: 198.09; Mol. Wt.: 198.22; C,
60.59; H, 7.12; O, 32.29.

The following Table 1 summarizes the op-
tional first step of the present synthetic sequence,
i.e., protecting the hydroxy group of compound (1)
to provide a protected compound (2).

Table 1. Preparation of Protected Compounds		
Product	Protecting Group	Yield (%)
2a	TBDMS	100
2b	TMS[a]	(b)
2c	COCH$_3$	100
2d	COt-Bu	93
2e	COPh	85
2f	THP	78
2g	MOM	82

[a] TMS is trimethylsilanyl.

[b] Complete conversion, product was used crude in next step of
the synthetic sequence.

Compound (1) or a protected compound (2)
then is subjected to a photochemical reaction with a
compound having heteroatoms. In the synthetic route
to bis-THF, compound (1) or a protected compound (2)
is reacted with 1,3-dioxolane. As discussed here-
after, compounds other than 1,3-dioxolane can be
utilized to synthesize bicyclic compounds related to
bis-THF.

The general procedure for the photoaddition of 1,3-dioxolane to compound (1) or a hydroxy-protected compound (2) to provide a compound (3) is as follows:

General procedure for the photoaddition of [1,3]-dioxolane to compound (1) or a protected compound (2):

A solution containing compound (1) or a protected compound (2) and benzophenone in [1,3]-dioxolane was degassed for 1 hour in a stream of argon. The reaction flask then was placed in a water-cooled cooling mantel. After the solution was cooled to the desired temperature, the solution was irradiated from a distance of 10 cm using one 450 watt ACE glass medium pressure mercury lamp. After the reaction was completed the solvent was evaporated and the residue purified by column chromatography.

The following examples illustrate the synthesis of a compound (3) from a compound (2).

5-(tert-Butyldimethylsilanyloxymethyl)-4-[1,3]dioxolan-2-yl-dehydro-furan-2-one (3a)
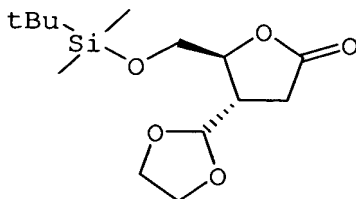
(4S,5S)-5-(tert-Butyldimethylsilanyloxy-methyl)-4-[1,3]dioxolan-2-yldihydrofuran-2-one (3a): A solution containing 228 mg (0.998 mmol) compound (2a) and 18.0 mg (0.998 mmol) benzophenone in 200 mL [1,3]-dioxolane was irradiated at 20°C for 5 hours according to the general procedure. Column chromatography (silica gel 35 g, ethyl acetate in hexanes 30%) gave compound (3a) (285 mg, 94%) as a colorless solid, R_f=0.35, $[\alpha]^{25}_D$ 18.3°, c 1.3, CHCl$_3$, IR (neat) 2953, 2857, 1778, 1125 cm^{-1}; ^{1}H-NMR (300 MHz, CDCl$_3$) δ: 0.05 (s, 6H), 0.87 (s, 9H), 2.45 (dd, 1H, J=4.2 Hz, J=17.7 Hz), 2.68 (d, 1H, J=17.7 Hz), 2.72-2.79 (m, 1H), 3.65 (dd, 1H, J=2.7 Hz, J=11.4 Hz), 3.86-3.91 (m, 3H), 3.97-4.01 (m, 2H), 4.50 (m$_c$, 1H), 4.88 (d, 1H, J=3.6 Hz). ^{13}C-NMR (75.4 MHz, CDCl$_3$, Dept) δ: 5.52 (+), 18.18 (quat), 25.77 (+), 30.12 (-), 39.67 (+), 64.71 (-), 65.36 (-), 65.47 (-), 80.24 (+), 103.94 (+), 176.55 (quat). C$_{14}$H$_{26}$O$_5$Si; Exact Mass: 302.15; Mol. Wt.: 302.44; C, 55.60, H, 8.67, O, 26.45, Si, 9.29.
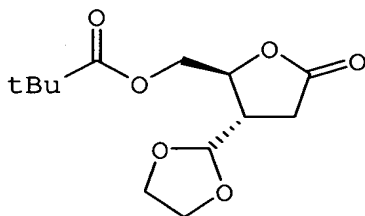
**(4S,5S)-5-(Acetyloxymethyl)-4-[1,3]
· dioxolan-2-yldihydrofuran-2-one (3c)**
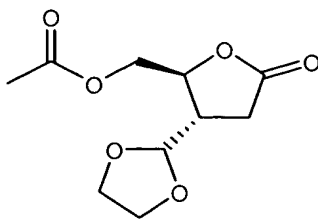
(4S,5S)-5-(Acetyloxymethyl)-4-[1,3]di-oxolan-2-yldihydrofuran-2-one (3c): A solution

containing 1.20 g (7.69 mmol) of compound (2c) and 107 mg (0.587 mmol) benzophenone in 230 mL [1,3]-dioxolane was irradiated at 0°C for 8.5 hours according to the general procedure. Column chromatography (silica gel 120 g, ethyl acetate in hexanes 50%) gave compound (3c) (1.63 mg. 92%) as a colorless solid, R_f=0.32, $[\alpha]^{25}_D$ 36.2°, c 1.3, $CHCl_3$, IR (neat) 1780, 1745, 1216, 759 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.08 (s, 3H), 2.52 (dd, 1H, J=10.4 Hz, J=21.7 Hz), 2.61-2.66 (m, 2H), 3.84-3.88 (m, 2H), 3.94-3.98 (m, 2H), 4.09 (dd, 1H, J=5.0 Hz, J=12.3 Hz), 4.32 (dd, 1H, J=2.9 Hz, J=12.3 Hz), 4.62 (m_c, 1H), 4.87 (d, 1H, J=3.6 Hz). ^{13}C-NMR (125.8 MHz, $CDCl_3$, Dept) δ: 21.11 (+), 30.16 (−), 40.45 (+), 65.65 (−), 65.78 (−), 65.91 (−), 77.82 (+), 103.54 (+), 170.91 (quat), 175.88 (quat). $C_{10}H_{14}O_6$; Exact Mass: 230.08; Mol. Wt.: 230.21; C, 52.17; H, 6.13; O, 41.70.

2,2-Dimethylpropionic acid 3-[1,3]dioxolan-2-yl-5-oxo-tetrahydrofuran-2-ylmethyl ester (3d)

(4S,5S)-5-(Pivaloyloxymethyl)-4-[1,3]di-oxolan-2-yldihydrofuran-2-one (3d). A solution containing 29.0 mg (0.146 mmol) compound (2d) and 3.0

mg (0.016 mmol) benzophenone in 20 mL [1,3]-dioxolane was irradiated at 0°C for 1.5 hours according to the general procedure. Column chromatography (silica gel 15 g, ethyl acetate in hexanes 40%) gave compound (3d) (37 mg. 93%) as a colorless solid, R_f=0.21, $[\alpha]^{25}_D$ 23.8°, c 1.0, $CHCl_3$, IR (neat) 1785, 1740, 1210, 740 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.21 (s, 9H), 2.57-2.60 (m, 1H), 2.67-2.75 (m, 2H), 3.91-3.93 (m, 2H), 4.01-4.04 (m, 2H), 4.37 (dd, 1H, J=4.2 Hz, J=12.2 Hz), 4.38 (dd, 1H, J=2.9 Hz, J=12.2 Hz), 4.69 (m$_c$, 1H), 4.92 (d, 1H, J=3.6 Hz). ^{13}C-NMR (100.6 MHz, $CDCl_3$, Dept) δ: 27.14 (+), 29.75 (-), 38.70 (+) (quat), 65.26 (-), 65.43 (-), 65.58 (-), 77.37 (+), 103.30 (+), 175.47 (quat), 178.02 (quat). $C_{13}H_{20}O_6$; Exact Mass: 272.13; Mol. Wt.: 272.29; C, 57.34, H, 7.40, O, 35.25.

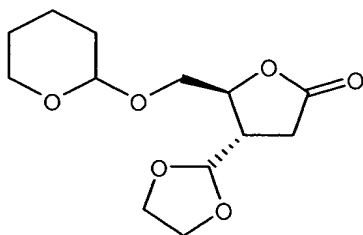### (4S,5S)-5-(Benzoyloxymethyl)-4-[1,3]-dioxolan-2-yldihydrofuran-2-one (3e)
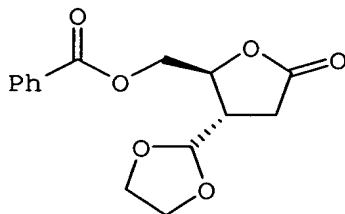
(4S,5S)-5-(Benzoyloxymethyl)-4-[1,3]dioxolan-2-yldihydrofuran-2-one (3e). A solution containing 180 mg (0.825 mmol) compound (2e) and 22.5 mg (0.123 mmol) benzophenone in 110 mL [1,3]-dioxolane was irradiated at 20°C for 7 hours according to the general procedure. Column chromatography (silica gel 40 g, ethyl acetate in hexanes 40%) gave

compound (3e) (193 mg. 80%) as a colorless solid,
R_f=0.29, $[\alpha]^{25}_D$ 35.2°, c 1.2, $CHCl_3$, IR (neat) 2360,
2342, 1779, 1721, 1272, 1118 cm^{-1}; ^{1}H-NMR (400 MHz,
$CDCl_3$) δ: 2.53 (d, 1H J=11.6 Hz), 2.62-2.73 (m, 2H),
3.83 (m_c, 2H), 3.94 (m_c, 2H), 4.37 (dd, 1H, J=5.1 Hz,
J=12.3 Hz), 4.53 (dd, 1H, J=2.9 Hz, J=12.3 Hz), 4.74
(ddd, 1H, J=2.9 Hz, J=5.1 Hz, J=6.9 Hz), 4.88 (d,
1H, J=3.4 Hz), 7.37 (dd, 2H, J=7.7 Hz, J=7.9 Hz),
7.49 (dd, 1H, J=1.0 Hz, J=7.7 Hz), 7.92 (dd, 2H,
J=1.0 Hz, J=7.9 Hz). ^{13}C-NMR (100.6 MHz, $CDCl_3$,
Dept) δ: 29.77 (-), 40.06 (+), 65.37 (-), 65.50 (-
), 65.99 (-), 77.56 (+), 103.14 (+), 128.51 (+),
129.31 (quat), 129.57 (+), 133.30 (+), 166.00 (quat)
175.62 (quat). $C_{15}H_{16}O_6$; Exact Mass: 292.09; Mol.
Wt.: 292.28; C, 61.64, H, 5.52, O, 32.84.

4-[1,3]Dioxolan-2-yl-5-(tetrahydropyran-2-yloxymethyl)-dihydrofuran-2-one (3f)

(4S,5S)-4-([1,3]Dioxolan-2-yl)-5-(tetra-
hydropyran-2-yloxymethyl)-dihydrofuran-2-one (3f):
A solution containing 136 mg (0.686 mmol) compound
(2f) and 18.7 mg (0.103 mmol) benzophenone in 100 mL
[1,3]-dioxolane was irradiated at 20°C for 5.75
hours according to the general procedure. Column
chromatography (silica gel 40 g, ethyl acetate in

hexanes 60%) gave compound (3f) as two diastereomers
(170 mg, 91%) as a colorless oil, $R_f=0.25$, $[\alpha]^{25}_D$ –
129°, c 0.8, $CHCl_3$. ^{1}H-NMR (300 MHz, $CDCl_3$) δ:
1.38–1.82 (m, 6H), 2.40–2.46 (m, 1H), 2.60–2.75 (m,
2H), 3.39–3.48 (m, 1H), 3.61–3.70 (m, 1H), 3.75–3.81
(m, 2H), 3.84–3.87 (m, 2H), 3.93–3.98 (m, 2H), 4.53–
4.63 (m, 2H), 4.86–4.89 (m, 1H). ^{13}C-NMR (75.4 MHz,
$CDCl_3$, Dept) diastereomer A: δ: 18.72 (–), 25.20 (–
), 29.98 (–), 30.02 (–), 40.08 (+), 61.52 (–), 64.68
(–), 65.33 (–), 68.33 (–), 78.98 (+), 98.21 (+),
103.64 (+), 176.51 (quat); B: δ: 19.23 (–), 25.20
(–), 30.21 (–), 30.24 (–), 40.08 (+), 62.20 (–),
65.05 (–), 65.45 (–), 68.81 (–), 79.08 (+), 99.09
(+), 103.71 (+), 176.72 (quat). $C_{13}H_{20}O_6$; Exact Mass:
272.13; Mol. Wt.: 272.29; C, 57.34; H, 7.40; O,
35.25.

The following Table 2 summarizes the prep-
aration of a compound (3) from a protected compound
(2).

Protecting Group	Yield of (3) (%)	d.r.[d]	% of Ph$_2$CO	Reaction conditions	Yield of a Compound (4) (%)[b]	Yield of a Compound (5) (%)
None (H)	Not isolated	94:6	100	[1,3]-dioxolane 20°C, 7h	89	69
TBDMS	36	76:24	150	20°C, 4.25 h		
TBDMS	79	96:4	10	20°C, 5h		
TBDMS	94	97:3	10	20°C, 5h	98	81
TBDMS	Pro+dec[a]	--	--	20°C, 5h		
TMS	50	96:4	8	6°C, 3h		
COCH$_3$	Pro+bypr[b]	--	8	20°C, 3.75 h		
COCH$_3$	90	94:6	9	20°C, 1h		
COCH$_3$				20°C, 1h, toluene:[1,3]-dioxolane 3:1		
COCH$_3$	91	96:4	8	6°C, 6h[c]	87	56
COPh				20°C, 5.75 h		
THP	91	96:4	15	20°C, 5.75 h	95 66	68
MOM	--	--	100	[1,3]-dioxolane, 20°C, 5h		
MOM	--	--	100	[1,3]-dioxolane, 20°C, 7h		

a   no further investigation, due to product decomposition or by-product formation.

b   yield of the crude product; crude product was used directly for cyclization.

c   large scale, therefore, longer reaction time was necessary.

d   d.r. is diastereomeric ratio.

In the next step of the present method, a compound (3) is reduced to provide compound (4), followed by a cyclization reaction to provide compound (5) using the following general procedure.

5   *General Procedure for the reduction of a compound (3) followed by cyclization to give (3S,3aS,6aR)-3-hydroxyhexahydrofuro[2,3-b]furan (compound (5)):*

To a solution of lithium aluminum hydride
10   in Et$_2$O or THF was added a solution of a compound (3) in THF, dropwise at 0°C. After 2 hours, the reaction was quenched at 0°C with an aqueous saturated Na$_2$SO$_4$ solution. The solvent was decanted and the remaining precipitate was washed with THF (3x),
15   ethyl acetate (3x), and CHCl$_3$ (3x). The combined organic extracts were dried over Na$_2$SO$_4$. Evaporation of the solvent gave a protected (2S,3S)-3-[1,3]di-oxolan-2-ylpentane-1,2,5-triol (compound 4), which was immediately used crude in the next reaction.
20   Compound 4 was dissolved in a mixture THF:water (5:1). At room temperature, the solution was acidified to pH 2-3 with 1N hydrochloric acid. After the reaction was complete, the organic layer was separated. The aqueous layer was extracted with
25   ethyl acetate (3 x 50 mL), and a solution of 70% CHCl$_3$, 20% MeOH, and 10% H$_2$O (3 x 50 mL). The combined organic extracts were dried over Na$_2$SO$_4$, the solvent was evaporated, and the residue was purified by column chromatography.

Hexahydrofuro[2,3-b]furan-3-ol (5)
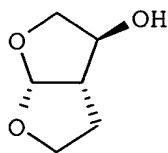
5   (3S,3aS,6aR)-3-Hydroxyhexahydrofuro[2,3-
b]furan (5): According to the above general pro-
cedure, a solution containing 216 mg (0.714 mmol)
(4S,5S)-5-(tert-butyldimethylsilanyloxymethyl)-4-
[1,3]-dioxolan-2-yldihydrofuran-2-one (3a) in THF
10   (25 mL) was reduced with 98 mg (2.58 mmol) LiAlH$_4$ in
THF (7 mL) to give the crude protected triol (4)
(132 mg, 96%). The crude triol (4) (76 mg (0.40
mmol)) was cyclized in 6 mL acidified THF:water
(5:1). Column chromatography (silica gel 20 g,
15   ethyl methanol in CH$_2$Cl$_2$ 10%) gave compound (5) (37.6
mg, 84%) as a colorless solid, R$_f$=0.35, $[\alpha]^{25}_D$ -25°, c
1.0, MeOH. ^{1}H-NMR (400 MHz, CDCl$_3$) δ: 1.67 (m$_c$,
1H), 2.14 (m$_c$, 1H), 2.63 (bs, 1H), 2.79 (m$_c$, 1H),
3.75-3.88 (m, 3H), 3.94 (dd, 1H, J=3.0 Hz, J=10.2
20   Hz), 4.20 (d, 1H, J=2.7 Hz), 5.86 (d, 1H, J=4.9 Hz).
^{13}C-NMR (125.8 MHz, CDCl$_3$, Dept) δ: 29.19 (-), 52.38
(+), 69.52 (-), 75.60 (-), 78.14 (=), 109.23 (+).
C$_6$H$_{10}$O$_3$; Exact Mass: 130.06; Mol. Wt.: 130.14; C,
55.37; H, 7.74; O, 36.88.

25   (3S,3aS,6aR)-3-Hydroxyhexahydrofuro[2,3-
b]furan (5): According to the above general pro-
cedure, a solution containing 1.44 mg (6.26 mmol)
(4S,5S)-5-(acetyloxymethyl)-4-[1,3]dioxolan-2-yldi-
hydrofuran-2-one (3c) in Et$_2$O:THF 1:1 (20 mL) was

reduced with 522 mg (13.75 mmol) LiAlH$_4$ in Et$_2$O (100 mL) to give the crude protected triol (4) (1.12 mg, 93%). The crude triol (4) was cyclized in 60 mL THF water (5:1) and 5 mL 1N hydrochloric acid. Column

5   chromatography (silica gel 20 g, ethyl methanol in CHCl$_3$ 10%) gave compound (5) (515 mg, 64%) as a colorless solid, R$_f$=0.35, [α]^{25}$_D$ -25.1°, c 1.0, MeOH.

Table 2 summarizes the preparation of com-

10   pounds (4) and (5) from a compound (3).

Tetrahydrofuro[2,3-b]furan-3-one (6)
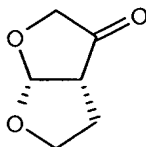
15   (3aS,6aR)-3-Oxyhexahydrofuro[2,3-b]furan (6): Under a nitrogen atmosphere, a solution containing 440 mg (3.38 mmol) (3S,3aS,6aR)-3-hydroxy-hexahydrofuro[2,3-b]furan (5), 599 mg (5.11 mmol) 4-methylmorpholine-N-oxide, and 2 g 4 Å molecular

20   sieves in CH$_2$Cl$_2$ (30 mL) was stirred for 20 minutes. Then, tetrapropylammonium perruthenate (36 mg (0.10 mmol)) was added at room temperature. After 5-10 minutes, the reaction mixture was filtered through a pad of silica gel (5 g) with CH$_2$Cl$_2$ (100 mL). After

25   evaporation, column chromatography (silica gel 70 g, ethyl acetate in hexanes 40%) gave compound (6) (409 mg. 94%) as a colorless solid, R$_f$=0.3, [α]^{25}$_D$ -126.6°, c 0.8, CHCl$_3$, IR (Neat) 1758, 1658, 1023 cm^{-1}; ^{1}H-NMR

(400 MHz, CDCl$_3$) δ: 2.23 (m$_c$, 1H), 2.96 (dd, 1H, J=6.8 Hz, J=6.8 Hz), 3.79 (m$_c$, 1H), 3.99 (m, 1H), 4.11 (s, 2H), 6.02 (d, 1H, J=5.0 Hz). ^{13}C-NMR (100.6 MHz, CDCl$_3$, Dept) δ: 30.38 (-), 49.58 (+), 67.65 (-), 71.69 (-), 107.89 (+), 215.52 (quat). C$_6$H$_8$O$_3$; Exact Mass: 128.05; Mol. Wt.: 128.13; C, 56.24, H, 6.29, O, 37.46.

(3R,3aS,6aR)-3-Hydroxyhexahydrofuro[2,3-b]furan (I)
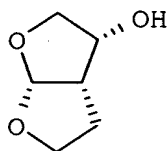
(3R,3aS,6aR)-3-Hydroxyhexahydrofuro[2,3-b]furan (I): To a solution containing 250 mg (1.95 mmol) (3aS,6aR)-3-oxyhexahydrofuro[2,3-b]furan (6) in EtOH (25 mL) was added 89 mg (2.35 mmol) NaBH$_4$ at -18°C. The reaction mixture was stirred at -18°C for 2.5 hours, then the reaction was quenched with saturated NH$_4$Cl solution (5 mL) and warmed to room temperature. The resulting mixture was concentrated under reduced pressure, and then 10 mL water was added. The aqueous layer was extracted with ethyl acetate (3 x 50 mL) and a solution of 70% CHCl$_3$, 20% MeOH, and 10% water (3 x 50 mL). The combined organic extracts were dried over Na$_2$SO$_4$. Column chromatography (silica gel 80 g, MeOH in CHCl$_3$ 7%) gave compound (I) (178 mg. 70%) as a colorless solid, R$_f$=0.3, [α]$^{25}_D$ -12.4°, c 1.3, MeOH. IR (neat) 2951, 1641, 1211 cm^{-1}; ^{1}H-NMR (400 MHz CDCl$_3$) δ: 1.85

(m_c, 1H), 1.94 (bs, 1H), 2.27 (m_c, 1H), 2.84 (m_c, 1H), 3.63 (dd, 1H, J=7.1 Hz, J=9.2 Hz), 3.89 (m_c, 1H), 3.97 (m_c, 1H), 4.43 (dd, 1H, J=6.8 Hz, J=14.5 Hz), 5.68 (d, 1H, J=5.2 Hz). ^{13}C-NMR (125.8 MHz, CDCl$_3$, Dept) δ: 25.27 (-), 46.97 (+), 70.31 (-), 71.26 (-), 73.50 (+), 109.93 (+). $C_6H_{10}O_3$; Exact Mass: 130.06; Mol. Wt.: 130.14; C, 55.37, H, 7.74, O, 36.88.
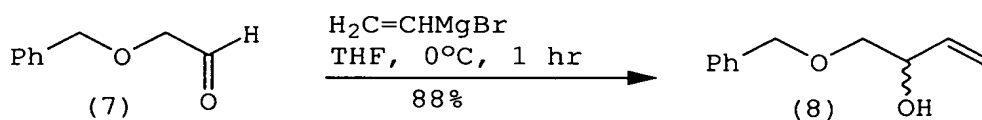
The following synthetic scheme illustrates the synthesis of another protected furan-2-one, i.e., compound (13), and an alternative synthesis of bis-THF (I) from compound (5). An important intermediate, i.e., racemic allylic alcohol (8), was prepared in multigram quantities by treatment of commercially available benzyloxyacetaldehyde (7) with vinylmagnesium bromide in THF at 0°C for 1 hour. Enzymatic acylation of the racemic alcohol (8) with immobilized lipase PS-30 (25% by weight with respect to lipase PS-30) in the presence of isopropenyl acetate in dimethoxyethane (DME) at 23°C for 23 hours provided the best yield. These conditions provided the optically active desired enantiomer (9) (43% yield, >99% ee) and the acylated alcohol 10 (54% yield), which were separated by silica gel chromatography as set forth in the following synthetic scheme. The optical purity of compound (9) was determined by formation of the Mosher ester and ^{19}F-NMR analysis (J.A. Dale et al., *J. Org. Chem., 34,* 2543 (1969)). A control experiment without the enzyme proved that the nonenzymatic reaction

was extremely slow (i.e., only trace amount of acyl-
ated product was formed after 48 hours at 23°C).
The acetate (10) can be readily converted to 2-(S)-
1-benzyloxy-but-3-en-2-ol (9) using a three-step
5   sequence including: (1) saponification of compound
(10) with K_2CO_3 in MeOH at 23°C for 35 minutes to
provide (R)-1-benzyloxy-but-3-en-2-ol (11); (2)
Mitsunobu inversion (S.F. Martin et al., *Tetrahedron
Lett., 32,* 3017 (1991) and O. Mitsunobu, *Synthesis*
10   (1981)) of the resulting 2-(*R*)-alcohol with Ph_3P, *p*-
NO_2-benzoic acid in the presence of diisopropylazodi-
carboxylate (DIAD) at 23°C for 40 minutes; and (3)
aqueous lithium hydroxide promoted saponification of
the resulting benzoate derivative. The (*S*)-alcohol
15 . (9) thus obtained (87% overall in 3 steps) has high
optical purity (>96% ee) after formation of the
Mosher ester and ^{19}F-NMR analysis. The absolute con-
figurations of the resolved alcohols were assigned
based upon comparison of optical rotation with the
20   literature data (A.V. Rao et al., *Tetrahedron Lett.,
26,* 2497-6500 (1987)).

Optically active allylic alcohol (9) was
converted to acrylate ester (12) by reaction with
acryloyl chloride and Et_3N in CH_2Cl_2 at 0°C for 10
25   minutes. Acrylate ester (12) was isolated in 92%
yield after silica gel chromatography. Olefin meta-
thesis of (12) with commercially available Grubbs'
second generation catalyst ($Cl_2(PCy_3)(IMes)Ru=CHPh$, 4
mol%) in refluxing CH_2Cl_2 for 5 hours, provided the
30   α,β-unsaturated γ-lactone (13) in 98% yield (R.H.
Grubbs et al., *Tetrahedron, 54,* 4413 (1998)).

Irradiation of compound (13) in the presence of 1,3-dioxolane and a catalytic amount of benzophenone using 450 watt mercury lamp for 9 hours provided dioxolane derivative (14) in 82% yield. Catalytic hydrogenation of compound (14) over 10% Pd-C in MeOH afforded alcohol (15) in 89% yield. Reduction of compound (15) with lithium aluminum hydride followed by acid catalyzed cyclization furnished bis-tetrahydrofuran derivative (5) in 77% yield in 2-steps. TPAP oxidation of compound (5) provided compound (6) which was reduced with sodium borohydride (NaBH$_4$) to provide optically active bis-tetrahydrofuranyl alcohol (I) as described previously.

$$Ph\diagup O \diagup CHO \quad (7) \qquad \xrightarrow[\quad 88\% \quad]{\substack{H_2C=CHMgBr \\ THF, \ 0°C, \ 1 \ hr}} \qquad Ph\diagup O \diagup CH(OH)CH=CH_2 \quad (8)$$
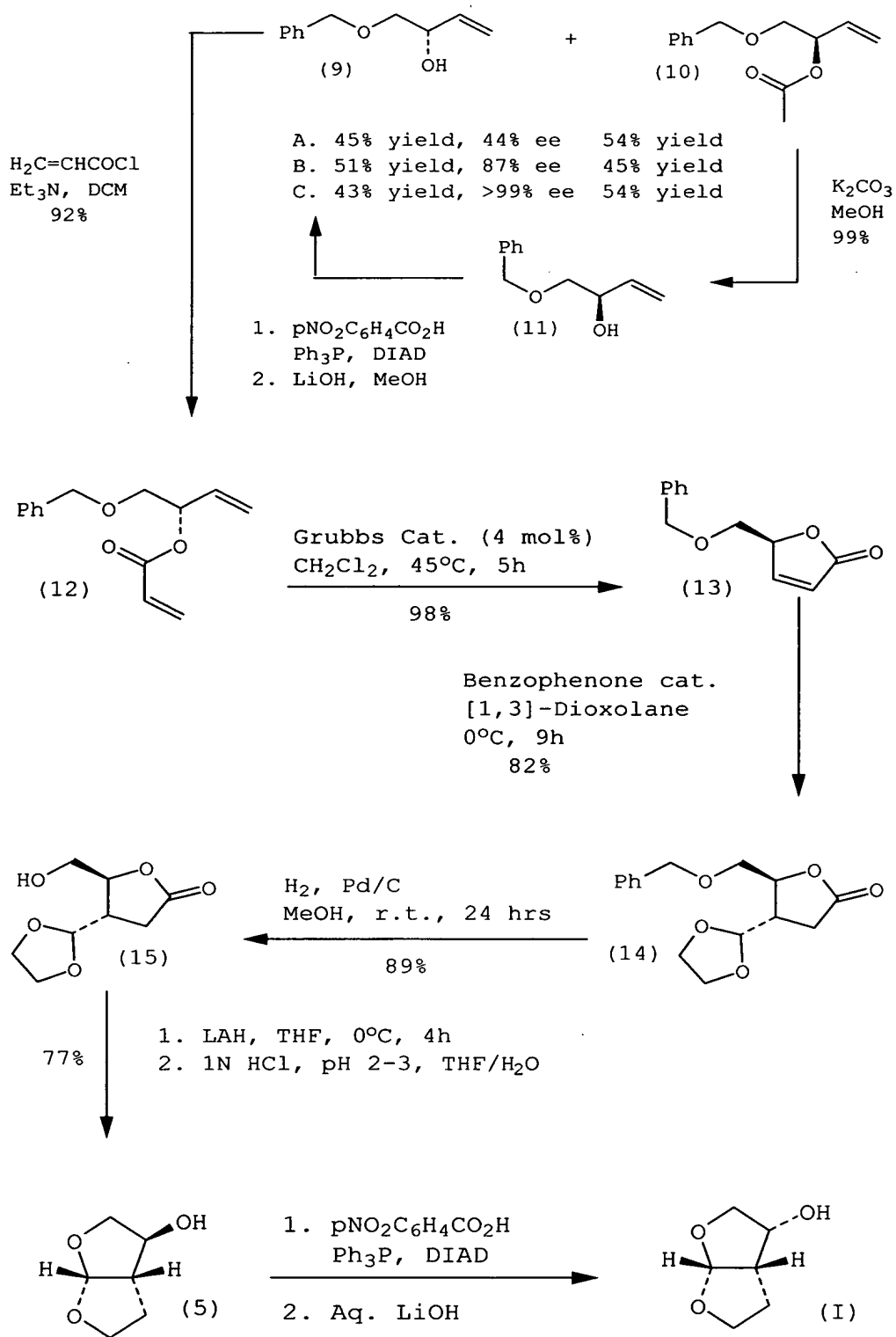
A. Lipase PS-30 on Celite 521
   (CH$_3$CO)$_2$O
   r.t., 20 hrs;

B. Lipase PS-30 on Celite 545
   CH$_3$CO$_2$CH=CH$_2$
   DME, r.t., 28 hrs

C. Lipase PS-30 on Celite
   CH$_3$CO$_2$C(CH$_3$)=CH$_2$
   DME, r.t., 23 hrs

PhCH₂O—CH₂—CH(OH)—CH=CH₂
(9)

+

PhCH₂O—CH₂—CH(OAc)—CH=CH₂
(10)

A. 45% yield, 44% ee   54% yield
B. 51% yield, 87% ee   45% yield
C. 43% yield, >99% ee   54% yield

H₂C=CHCOCl
Et₃N, DCM
92%

K₂CO₃
MeOH
99%

1. pNO₂C₆H₄CO₂H
   Ph₃P, DIAD
2. LiOH, MeOH

Ph—CH₂—O—CH₂—CH(OH)—CH=CH₂
(11)

(12)

Grubbs Cat. (4 mol%)
CH₂Cl₂, 45°C, 5h
98%

(13)

Benzophenone cat.
[1,3]-Dioxolane
0°C, 9h
82%

(15)

H₂, Pd/C
MeOH, r.t., 24 hrs
89%

(14)

1. LAH, THF, 0°C, 4h
2. 1N HCl, pH 2-3, THF/H₂O

77%

(5)

1. pNO₂C₆H₄CO₂H
   Ph₃P, DIAD
2. Aq. LiOH

(I)

Epimeric alcohol (5) also was converted to desired bis-THF (I) using a two-step sequence involving: (1) Mitsunobu inversion of compound (5) using triphenylphosphine (Ph₃P) and *p*-nitrobenzoic acid in the presence of diisopropylazodicarboxylate and (2) aqueous lithium hydroxide promoted saponification of the resulting benzoate derivative to provide bis-THF (I).

Experimentals:

1-(Benzyloxy)-but-3-en-2-ol (±)-(8): To a solution of vinylmagnesium bromide (1 M in THF, 40 mL, 40 mmol) in THF (10 mL) at 0°C was added benzyloxyacetaldehyde (7) (5 g, 33.3 mmol) dropwise. The mixture was stirred for 10 min at 0°C, and the reaction then was quenched with 20 mL of saturated NaHCO₃ solution. The layers were separated, the aqueous layer was extracted with ethyl acetate (3 x 20 mL), and the combined organic extracts were dried over sodium sulfate. Evaporation of solvent under reduced pressure, followed by column chromatography on silica gel (20% EtOAc in hexanes as the eluent) yielded alcohol (±)-8 (5.22 g, 88%) as a yellow oil, R_f=0.40 (30% EtOAc in hexanes); ^{1}H-NMR (400 MHz, CDCl₃) δ: a 2.79 (bs, 1H), 3.39 (dd, 1H, J=1.7, 7.85 Hz), 3.55 (dd, 1H, J=3.35, 6.3 Hz), 4.35 (m, 1H), 4.58 (s, 1H), 5.21 (dt, 1H, J=7.75, 1.4 Hz), 5.38 (dt, 1H, J=14.18, 1.4 Hz), 5.84 (m, 1H), 7.30-7.38 (m, 5H); ^{13}C-NMR (100.6 MHz, CDCl₃) δ: 71.52, 73.37, 74.02, 116.49, 127.85, 128.49, 136.58, 137.81.

(S)-1-(Benzyloxy)-but-3-en-2-ol (9)   and
(R)-1-(benzyloxy)-but-3-en-2-oyl acetate (10):

A: To a solution of alcohol (±)-(8) (5.21
g, 29.3 mmol) in acetic anhydride (14 mL, 147 mmol)
and tert-butyl methyl ether (70 mL, 586 mmol) was
added immobilized lipase PS-30 (5.3 g) on Celite
521 (Aldrich). The mixture was stirred at room tem-
perature for 20 h, and then filtered through Celite.
Removal of solvent under reduced pressure followed,
by column chromatography on silica gel (10 and 15%
EtOAc in hexanes as the eluents) yielded acetate
(10) (3.81 g, 54%) R_f=0.57 (30% EtOAc in hexanes) as
a clear oil, $[\alpha]^{25}_D$ -2° (c 1, $CHCl_3$); NMR (500 MHz,
$CDCl_3$) δ: 2.10 (s, 3H), 3.55-3.59 (m, 2H), 4.56 (q,
2H, J=12.2, 14.0 Hz), 5.24 (d, 1H, J=10.6 Hz), 5.32
(d, 1H, J=17.3 Hz), 5.50 (m, 1H), 5.84 (m, 1H),
7.25-7.36 (m, 5H); ^{13}C-NMR (125.8 MHz, $CDCl_3$) δ:
21.62, 71.67, 73.57, 73.59, 118.39, 128.14, 128.84,
133.77, 138.32, 170.63; alcohol 9 (2.34 g, 45%) as a
yellow oil, R_f=0.40 (30% EtOAc in hexanes), $[\alpha]^{25}_D$-
8.3° (c 1.06, MeOH).

B: To a solution of alcohol (±)-(8) (3.92
g, 22.0 mmol) in vinyl acetate (46 mL, 499 mmol) and
ethylene glycol dimethyl ether (46 mL, 440 mmol) was
added immobilized lipase PS-30 (4 g) on Celite-545
(Aldrich). The mixture was stirred at room tempera-
ture for 28 h, and then filtered through celite.
Removal of solvent under reduced pressure, followed
by column chromatography on silica gel (10 and 15%
EtOAc in hexanes as the eluents) yielded acetate
(10) (2.20 g, 45%) R_f=0.57 (30% EtOAc in hexanes) as

a clear oil, $[\alpha]^{25}_D$ -2.7° (c 1.35, MeOH); alcohol (9) (2.00 g, 51%) as a yellow oil, R_f=0.40 (30% EtOAc in hexanes), $[\alpha]^{25}_D$ -11.4° (c 1.6, MeOH).

C: To a solution of alcohol (±)-(8) (30 mg, 0.168 mmol) in isopropenyl acetate (375 µL, 3.36 mmol) and ethylene glycol dimethyl ether (375 µL, 3.61mmol) was added immobilized lipase PS-30 (35 mg) on Celite-545 (Aldrich). The mixture was stirred at room temperature for 23 h, and then filtered through celite. Removal of solvent under reduced pressure, followed by column chromatography on silica gel (10) and 15% EtOAc in hexanes as the eluents) yielded acetate 10 (20.3 mg, 54%) as an oil, R_f=0.57 (30% EtOAc in hexanes), $[\alpha]^{25}_D$ -1.4° (c 1.02, MeOH); alcohol (9) (13 mg, 43%) as a yellow oil, R_f=0.40 (30% EtOAc in hexanes), $[\alpha]^{25}_D$ -13.5° (c 1.3, MeOH).

(R)-1-(Benzyloxy)-but-3-en-2-ol (11): To a solution of acetate (10) (3.7 g, 16.9 mmol) in methanol (20 mL) was added K_2CO_3 (7 g, 50.6 mmol). The mixture was stirred at room temperature for 35 min. Methanol then was removed under reduced pressure. The resulting solid residue was dissolved in ethyl acetate, washed with saturated NH_4Cl solution and brine, and dried over sodium sulfate. Removal of ethyl acetate under reduced pressure yielded the crude alcohol (11) (3 g, 100%) as a yellow oil, R_f=0.40 (30% EtOAc in hexanes), $[\alpha]^{25}_D$ 8.3° (c 1.06, MeOH).

(S)-1-(Benzyloxy)-but-3-en-2-ol (9) from (11): To a solution of crude alcohol (5) (2 g, 11.2 mmol), triphenylphosphine (5.88 g , 22.4 mmol), and

4-nitrobenzoic acid (2.81 g, 16.8 mmol) in benzene
(35 mL) was added at room temperature diisopropyl
azodicarboxylate (4.35 mL, 22.4 mmol) dropwise. The
mixture was stirred for 40 min, followed by the re-

5 moval of solvent under reduced pressure. All of the
crude ester then was dissolved in a mixture of
MeOH:Et$_3$N:H$_2$O (20ml) in the ratio of 4:3:1 and re-
acted with LiOH (1.64 g, 39.3 mmol) at room tempera-
ture. The mixture was stirred for 2 h, followed by

10 the removal of solvent. Column chromatography on
silica gel (15% EtOAc in hexanes as the eluent)
yielded alcohol (3) (1.64 g, 82%) as a yellow oil,
R$_f$=0.40 (30% EtOAc in hexanes), $[\alpha]^{25}_D$ -7.3° (c 0.82,
MeOH).

15   **(S)-1-(Benzyloxy)-but-3-en-2-yl acrylate**
(12): To a solution of alcohol (3) (1 g, 5.61 mmol)
in CH$_2$Cl$_2$ (20 mL) was added acryloyl chloride (685
μL, 8.41 mmol) dropwise, followed by the addition of
Et$_3$N (1.56 mL, 11.2 mmol). The resulting mixture was

20 stirred for 10 min, and the solvent then was removed
under reduced pressure. Filtration of the concen-
trated crude acrylate through a pad of silica gel
using 15% EtOAc in hexanes, followed by the removal
of solvent, yielded acrylate (12) (1.19 g, 92%) as a

25 colorless oil, R$_f$=0.57 (30% EtOAc in hexanes), $[\alpha]^{25}_D$
-5.7° (c 1.09, CHCl$_3$); ^{1}H-NMR (500 MHz, CDCl$_3$) δ:
3.59-3.65 (m, 2H), 4.56 (q, 2H, J=12.2, 14.65 Hz),
5.25 (d, 1H, J=10.6 Hz), 5.33 (d, 1H, J=16.8 Hz),
5.57 (m, 1H), 5.84-5.91 (m, 2H), 6.17 (dd, 1H,

30 J=6.9, 10.4 Hz), 6.44 (dd, 1H, J=1.3, 16.2 Hz),
7.27-7.36 (m, 5H); ^{13}C-NMR (125.8 MHz, CDCl$_3$) δ:

71.62, 73.58, 73.77, 118.49, 128.05, 128.85, 131.52, 133.62, 138.31, 165.79.

(5S)-5-(Benzyloxymethyl)-5H-furan-2-one

(13): To a solution of acrylate (12) (1.87 g, 8.05 mmol) in CH_2Cl_2 (700 mL) was added second generation Grubbs' catalyst (4 mol %, 170 mg, 0.322 mmol). The reaction mixture was refluxed for 5 hours, and the solvent then was removed under reduced pressure. Column chromatography on silica gel (30% EtOAc in hexanes as the eluent) yielded the furanone (13) (1.62 g, 98%) as a brown oil, R_f=0.15 (30% EtOAc in hexanes), $[\alpha]^{25}_D$ -81.3° (c 1.09, MeOH); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.66 (dd, 1H, J=5.0, 5.5 Hz), 3.71 (dd, 1H, J=5.0, 5.2 Hz), 4.57 (s, 2H), 5.17 (m, 1H), 6.16 (dd, 1H, J=1.9, 3.8 Hz), 7.29-7.37 (m, 5H), 7.48 (dd, 1H, J=1.4, 4.3 Hz); ^{13}C-NMR (125.8 MHz, $CDCl_3$) δ: a 69.86, 74.18, 82.61, 123.03, 128.42, 128.95, 137.69, 154.32, 173.19.

(4S,5S)-5-(Benzyloxymethyl)-4-[1,3]di-oxolan-2-yldihydrofuran-2-one (14): A solution of

furanone (13) (1.2 g, 5.88 mmols) and benzophenone (108 mg, 0.588 mmols) in [1,3]-dioxolane (108 mg) was degassed for 40 min in a stream of argon. The mixture then was irradiated using one 450 watt ACE glass medium pressure mercury lamp, from a distance of 15 cm, for 9 hours. Progress of this reaction was observed via ^{1}H-NMR. As the reaction mixture was degassed, and throughout all of the irradiation time, the reaction flask was held in a water cooled cooling mantel. The temperature of the cooling water was constantly maintained near 0°C. Upon

completion of the reaction, solvent was removed
under reduced pressure, followed by column chroma-
tography on silica gel (35% EtOAc in hexanes as the
eluent), yielding the title compound (1.34 g, 82%)
as a clear oil, R_f=0.14 (30% EtOAc in hexanes), $[\alpha]^{25}_D$
16.5° (c 1.2, CHCl$_3$); ^{1}H-NMR (500 MHz, CDCl$_3$) δ:
2.50 (dd, 1H, J=3.9, 12.9 Hz), 2.70-2.79 (m, 2H),
3.58 (dd, 1H, J=3.5, 7.2 Hz), 3.75 (dd, 1H, J=2.8,
7.9 Hz), 3.87-3.92 (m, 2H), 3.97-4.00 (m, 2H), 4.51
(d, 1H, J=11.9 Hz), 4.57-4.61 (m, 2H), 4.88 (d, 1H,
J=3.6 Hz), 7.26-7.36 (m, 5H); ^{13}C-NMR (125.8 MHz,
CDCl$_3$) δ: 30.39, 40.53, 65.77, 71.74, 73.99, 79.52,
104.14, 128.00, 128.89, 138.07, 176.79.

**(4S,5S)-4-[1,3]Dioxolan-2-yl-5-hydroxy-
methyldihydrofuran-2-one (15):** To a solution of
dihydrofuranone (14) (0.5 g, 1.79 mmol) in MeOH (30
mL) was added Pd/C (25 mg). The mixture was stirred
at room temperature under an H$_2$ balloon for 24 hours,
and then filtered over Celite. Removal of solvent
under reduced pressure, followed by column chroma-
tography on silica gel (35% EtOAc in hexanes as the
eluent) yielded the compound (15) (301 mg, 89%) as a
white solid, R_f=0.28 (50% EtOAc in hexanes), $[\alpha]^{25}_D$
22° (c 1.32, CHCl$_3$); ^{1}H-NMR (500 MHz, CDCl$_3$) δ: 2.54
(dd, 1H, J=6.0, 11.4 Hz), 2.68-2.81 (m, 2H), 3.66
(dd, 1H, J=3.9-8.5 Hz), 3.88-3.95 (m, 3H), 3.97-4.02
(m, 2H), 4.53 (m, 1H), 4.91 (d, 1H, J=3.9 Hz); ^{13}C-
NMR (125.8 MHz, CDCl$_3$) δ: 30.68, 40.12, 64.36,
65.77, 81.07, 103.94, 176.83.

**(3S,3aS,6aR)-3-Hydroxyhexahydrofuro[2,3-
b]furan (5):** To a solution of lithium aluminum

hydride (76 mg, 1.98 mmols) in THF (10 ml) at 0°C
was added dihydrofuranone 15 (275 mg , 1.46 mmol) in
THF (30 mL) dropwise. Upon completion of the re-
duction after 4 hours, the reaction was quenched
5   with a saturated aqueous sodium sulfate solution at
0°C. The solvent then was decanted and the remain-
ing residue was washed with THF (3x), EtOAc (3x),
and $CHCl_3$ (3x). The organic extracts were combined
and the solvent was removed under reduced pressure,
10   yielding a crude (2S,3S)-3-[1,3]dioxolan-2-
ylpentane-1,2,5-triol, which was immediately used in
the next reaction.

The crude triol was dissolved in a mixture
of $THF:H_2O$ (8ml) in the ratio of a 5:1. This solu-
15   tion then was acidified at room temperature to pH 2-
3 with 1 N hydrochloric acid, and was stirred for 40
hours. Removal of solvent with the aid of benzene
under reduced pressure, followed by column chroma-
tography purification on silica gel (5% MeOH in $CHCl_3$
20   as the eluent) yielded the compound (5) (145 mg,
77%) as a white solid, R_f=0.40 (15% MeOH in $CHCl_3$),
$[\alpha]^{25}_D$ -25.1° (c 1.05, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$)
δ: 1.67 (m, 1H), 2.13 (m, 1H), 2.31 (bs, 1H), 2.79
(m, 1H), 3.80-3.88 (m, 3H), 3.95 (dd, 1H, J=3.2, 7.1
25   Hz), 4.20 (d, 1H, J=3.1 Hz), 5.86 (d, 1H, J=4.9 Hz).

**Preparation of bis-THF derivative (I) (by
Mitsunobu inversion of compound (5)):** To a stirred
solution of alcohol (5) (400 mg, 3.07 mmol), tri-
phenylphosphine (1.6 g, 61.4 mmol), and p-nitroben-
30   zoic acid (770 mg, 4.61 mmol) in dry benzene (30 mL)
at 23°C was added diisoproylazodicarboxylate (DIAD,

1.2 mL, 6.14 mmol) dropwise. After 1.5 hours, the mixture was concentrated *in vacuo*, and the crude ester was dissolved in a (4:3:1) mixture of $MeOH:Et_3N:H_2O$ (24 mL), then treated with LiOH (450 mg, 10.7 mmol). The solution was stirred at room temperature for 2 h. The mixture then was concentrated under reduced pressure and the residue was chromatographed over silica gel to provide the bis-THF (I) (326 mg, 82%); $[\alpha]^{25}_D$ -12.4 (c 1.16 , MeOH).

The present method also allows for the preparation of stereoisomers of bis-THF. In particular, by using (5R)-hydroxymethyl-5H-furan-2-one, having a structural formula

,
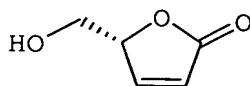
as the starting material in the present yields the following stereoisomers of bis-THF

     and
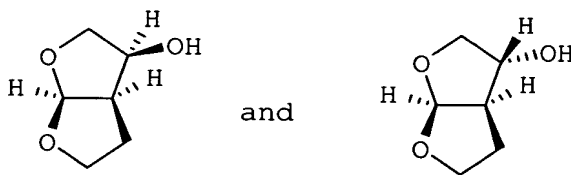
The present method also allows for the preparation of a substituted bis-THF or related bis-THF compound. In particular, the following synthesis illustrates the preparation of a methoxy-substituted derivative (Ia) from compound (1) using meth-

oxymethanol (MOM) as the protecting group in the
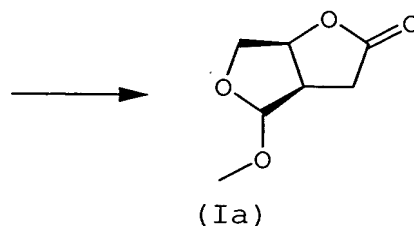method of the present invention.

(1)

(2g)

(Ia)
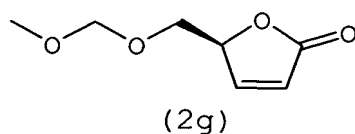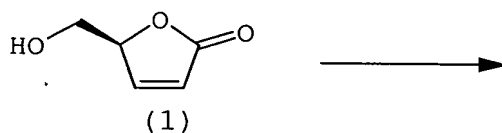
Table 3.   Preparation of Compound (Ia)

| % of Ph₂CO	Reaction conditions
--	AIBN, PhH, Δ:
100	PhH, hν, RT, 7 h
100	PhH, hν, 23°C, 7 h

PhH is benzene; AIBN is 2,2'-azobisisobutyronitrile.

In addition, compounds having the same
stereochemistry of compound (I), but different sub-
stituents, can be synthesized utilizing the method
of the present invention. For example, the follow-
ing compound can be prepared from compound (6) by a
reductive amination step.
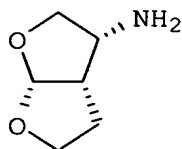
Compound (I) also can be interconverted to
a compound related to compound (I). An example of
an appropriate interconversion includes, but is not
limited to, hydroxy to alkoxy.

The present method also can be used to
synthesize bicyclic compounds related to bis-THF.
For example, utilizing the same procedure set forth
above to synthesize bis-THF, except substituting
1,3-dioxane for 1,3-dioxolane, yields compound (II),
stereoselectively, and in good yield. The method
also can be used to prepare enantiomers of compound
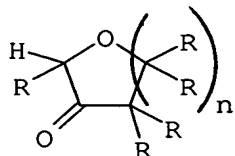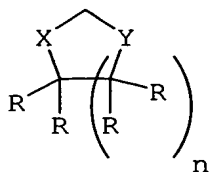(II) by a proper selection of starting materials and
reagents.
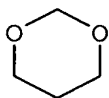
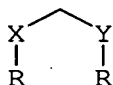1,3-dioxane   (II)
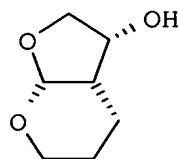
More generally, a cyclic or an acyclic
compound having the following general structural
formulae can be substituted for 1,3-dioxolane in the
present synthetic method:

5   , or

                                                                          ,

10   wherein X and Y, independently, are selec-
ted from the group consisting of O, S, and NR; each
R, independently, is selected from the group con-
sisting of hydro, C_{1-4}alkyl, aryl, C_{1-3}alkoxy, and
C_{1-2}alkylenearyl; and n is 1, 2, or 3. Typically, X
15   is O, and Y is O, X, or NR. The R group typically
is H, methyl, ethyl, phenyl, benzyl, or OCH_3.
        Substituting an above-described hetero-
atom-containing compound for 1,3-dioxolane provides
a compound having a general structural formula (IV).

20
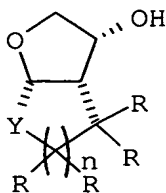
        (IV)

As used herein, the term "C_{1-4}alkyl" is defined herein as straight chained and branched hydrocarbon groups containing the indicated number of carbon atoms, i.e., methyl, ethyl, and straight

5   chain and branched propyl and butyl groups.

The term "alkylene" is defined herein as an alkyl group having a substituent. For example, the term "C_{1-3}alkylenearyl" refers to an alkyl group containing one to three carbon atoms, and substi-

10   tuted with an aryl group.

The term "aryl" is defined herein as a monocyclic or polycyclic aromatic group, preferably a monocyclic or bicyclic aromatic group, e.g., phenyl or naphthyl. An "aryl" group can be unsub-

15   stituted or substituted, for example, with one or more, and in particular one to three, halo, alkyl, alkoxy, alkoxyalkyl, haloalkyl, nitro, and cyano. Exemplary aryl groups include phenyl, naphthyl, tetrahydronaphthyl, chlorophenyl, methylphenyl,

20   methoxyphenyl, trifluoromethylphenyl, nitrophenyl, and the like.

The term "alkoxy" is defined herein as -OR', wherein R' is alkyl.

Modifications and variations of the inven-

25   tion as hereinbefore set forth can be made without departing from the spirit and scope thereof, and, therefore, only such limitations should be imposed as are indicated by the appended claims.